Objective: To clarify the cause, clinical course, and management of children with angioedema.

Design: Retrospective review.


Patients: Consecutive sample of all children hospitalized from January 1, 1987, to December 31, 1997, with the diagnosis of angioedema. Complete records permitting analysis were available for 10 patients.

Main Outcome Measures: Sex, age, site, symptoms at initial examination, cause, therapeutic management, and clinical outcome.

Results: Seven boys and 3 girls, a mean age of 7.7 years, had angioedema of the head or neck, most often facial (8/10 [80%]). Manifesting symptoms, in addition to swelling, were tenderness or pain in 4 children (40%), dyspnea in 3 (30%), dysphagia (including drooling and spitting) in 3 (30%), and hoarseness in 1 (10%). Angioedema was due to food in 4 children (40%), insect bites in 3 (30%), infection in 2 (20%), and an antibiotic in 1 (10%). Treatment was pharmacological in all cases. No child required intubation or tracheotomy. Care in the intensive care unit was necessary for 1 child (10%).

Conclusions: Pediatric angioedema exhibits a different cause and clinical manifestations than does adult angioedema. Prompt diagnosis and early treatment with an intravenous corticosteroid, an antihistamine, and/or epinephrine lead to rapid resolution and may, in appropriately staffed settings, avoid the need for care in the intensive care unit or airway intervention. Management algorithms based on adult experience must be modified to account for the milder pediatric manifestations of this immunologic disease.


Angioedema is an anatomically limited nonpitting edema that may result in life-threatening airway obstruction. Aside from the rarely seen but often discussed entity, hereditary angioedema, pediatric manifestations and management have not been described comprehensively. We reviewed our experience with angioedema to clarify the cause, clinical course, and management of this disease in children.

Thirteen children were admitted from January 1, 1987, to December 31, 1997, with the diagnosis of angioedema. The medical records of 3 children were excluded from the study: medical records were incomplete for 2 children, precluding analysis; for 1 child, a local reaction to an insect bite was erroneously recorded as angioedema. The study sample included 7 boys and 3 girls; the mean age was 7.7 years (range, 3-18 years). All children had angioedema of the head, neck, or both. Edema was present on the face in 8 children (80%), the lip in 4 (40%), the neck in 2 (20%), the tongue in 1 (10%), the uvula in 1 (10%), and the scalp in 1 (10%) (Figure 1). Two children (20%) also had swelling of the hand. A rash was noted in 5 children (50%). The manifesting symptoms in addition to swelling were tenderness or pain in 4 children (40%), dyspnea in 3 (30%), dysphagia (including drooling and spitting) in 3 (30%), and hoarseness in 1 (10%).

The angioedema was related to food in 4 children (40%), an insect bite in 3 (30%), an upper respiratory infection in 2 (20%), and an antibiotic in 1 (10%) (Figure 2).

The family history for 1 child (10%) revealed that the father may have experienced angioedema. The family could not be contacted for further follow-up.
METHODS

We performed a retrospective review of the medical records for children admitted from January 1, 1987, to December 31, 1997, with the diagnosis of angioedema at the Children’s Hospital of Philadelphia, Philadelphia, Pa. This consecutive sample was studied for sex, age, site, manifesting symptoms, cause, therapeutic management, and clinical outcome. Telephone follow-up was attempted for all cases.

The families of 3 children (30%) were contacted by telephone. None of the 3 children experienced further episodes of angioedema.

The medical history revealed reactive airways disease and eczema in 2 children (20%). Four children (40%) had allergies: 1 from environmental allergens, 1 with multiple food allergies, 1 had experienced angioedema due to the ingestion of nuts, and 1 had experienced similar reactions.

Laboratory tests were ordered for 3 children. The results of complete blood cell counts were normal for 2 children. Normal complement (C) 1 and C1 esterase inhibitor (C1-INH) levels and a moderately elevated erythrocyte sedimentation rate of 47 mm/h by the Westergren method (normal, <30 mm/h) were found for 1 child.

Antihistamines were required for the treatment of acute disease in 9 children (90%), corticosteroids in 6 (60%), and subcutaneous injection of epinephrine in 3 (30%). All children who received corticosteroids also received antihistamines. On discharge from the hospital, an epinephrine autoinjector was prescribed for 3 children (30%), antihistamines for 3 (30%), and oral corticosteroids for 3 (30%).

Nine children (90%) were treated on the hospital ward, while 1 (10%) required observation in the intensive care unit (ICU). No children required airway intervention by intubation or tracheotomy. The duration of hospitalization ranged from 1 to 5 days (mean, 2.6 days). All children were discharged to home.

COMMENT

The first description of angioedema in the Western medical literature is attributed to Robert Graves’ 1843 Clinical Lectures. As reported by Major,1 Graves wrote in his 1888 edition: “Sometimes the lips inside of the mouth, palate, and uvula are attacked, giving rise to a very considerable inconvenience. Were such tumors to occur in the neighborhood of the glottis, I need not say that they would be pregnant with danger of no ordinary character.”

Today we regard angioedema as an immunologically mediated, anatomically limited, nonpitting edema that up to 10% of the American population may experience during their lifetime.2 Angioedema is distinguished from the more common urticaria by the location of the edema and by the accompanying symptoms.

Angioedema manifests in the subcutaneous tissues, sometimes with prodromal tingling, paresthesias, or pruritus. Urticaria is a local reaction that manifests in the deep dermis and is always pruritic.

Angioedema affects men and women equally, usually during the third or fourth decade of life. Most angioedema manifests in the head and neck, usually on the face, lips, tongue, or larynx.3,4 Angioedema is caused by a kinin- and complement-mediated increase in vascular permeability. Most often, angioedema is due to trauma (including medical procedures), food, and medications. In rare cases, the unchecked propagation of the complement cascade results from a qualitative or quantitative defect in C1-INH. This disorder is termed hereditary angioedema. Hereditary angioedema usually manifests during childhood.6 Hereditary angioedema usually is transmitted in an autosomal codominant mode by an alteration in chromosome 11,7 although a spontaneous mutation rate up to 20% has been reported.8

Care of the patient with angioedema must heed airway and systemic signs. The possibility of central nervous system, abdominal, pulmonary, and gastrointestinal edema may require computed tomographic scanning with contrast for diagnosis,9 intravenous fluid for intravascular volume repletion, and diuresis or ventilatory support for treatment of pulmonary edema.10 Corticosteroid therapy using intravenous dexamethasone sodium phosphate or hydrocortisone remains the main treatment for angioedema. Tapered doses of oral corticosteroids are used for outpatient management of angio-
edema. Epinephrine (0.3 mL of a 1:1000 dilution, given subcutaneously, repeated up to 3 times) may be used to treat airway edema. Inhaled albuterol or terbutaline also have been used to treat airway symptoms. An antihistamine, such as diphenhydramine hydrochloride (Benadryl) or hydroxyzine (Atarax, Vistaril), is used to reduce pruritus and inflammation. Histamine type 2 blocking agents and gastric cytoprotective agents prevent stress- and corticosteroid-induced gastritis.

The high mortality of untreated hereditary angioedema—up to one third of patients formerly died of laryngeal edema—justifies long-term treatment for frequent episodes (more than twice a month) or airway compromise. Long-term therapy for patients with hereditary angioedema includes lyophilized C1-INH concentrate, aerosolized C1-INH, or fresh frozen plasma. Epsilon aminocaproic acid (Amicar) may be used for short- and long-term treatment of angioedema in children. The attenuated androgens, such as danazol and stanozolol, provide short- and long-term relief. An- drogens are used mostly for the treatment of angioedema in adults. While their use has been discouraged in pregnant women and children, limited pediatric experience has been successful. Patients must be warned that the side effects of androgens include weight gain, virilization, menstrual irregularities, and hypertension. Tonsillectomy may relieve oropharyngeal angioedema due to recurrent tonsillitis. Preoperative prophylaxis is possible with attenuated androgens, corticosteroids, fresh frozen plasma, epsilon aminocaproic acid, and C1-INH concentrate.

Staging the disease by anatomic site permits triage to appropriate care settings. Adults with facial, lip, and soft palate edema may be treated as outpatients or on the hospital ward, provided that adequate staffing and expertise are available to monitor patients’ conditions. Lingular and laryngeal edema usually require observation in the ICU. Occasionally, airway intervention by intubation or tracheotomy is required for patients with lingual or laryngeal edema.

Pediatric angioedema differs markedly in cause and severity from the adult form of the disease. Our experience with 10 children during the past decade permits us to make subjective rather than statistical comparisons with the earlier work with adults by one of us (U.K.S.).

We studied 10 children, 7 boys and 3 girls, who were treated at a mean age of 7.7 years. The small sample does not permit a detailed analysis of the incidence by sex in angioedema.

The children exhibited predominantly facial (80%) and lip (40%) edema (Figure 1). While the visualization of airway edema by flexible fiberoptic nasopharyngolaryngoscopy is ideal, it is not practical in all pediatric cases. The anatomic site of edema may be inferred reliably by symptoms. Five children (50%) in our group had signs or symptoms of hypopharyngeal or laryngeal edema: hoarseness, drooling, dyspnea, and dysphagia. None of the children underwent nasopharyngolaryngoscopy.

Food was the principal cause of angioedema (40%), followed by upper respiratory infection and insect bites. Antibiotics were responsible for only 1 episode of angioedema in our sample. Four children (40%) had allergic and immunologic disorders: eczema, reactive airways disease, multiple food allergies, and a previous episode of angioedema due to the ingestion of nuts, all of which indicate a predisposition to systemic immunologic disorders. One child’s father was thought to have had an episode of angioedema. While this child also experienced abdominal pain, consistent with hereditary angioedema, no laboratory evaluation was performed at the time of hospitalization. One child with known hereditary angioedema was identified after the study period. She underwent dental surgery under general anesthesia and was prophylactically treated with fresh frozen plasma and danazol. She experienced no perioperative angioedema and was discharged from the hospital to home the same day. The lack of children with hereditary angioedema in our review may indicate successful prophylaxis of children with known hereditary angioedema or an institutional referral bias.

The severity of angioedema is indicated retrospectively by the location of treatment (outpatient, ward, or ICU) and by the need for airway intervention. Only 1 child, who had asthma and had undergone renal transplantation, required treatment in the ICU setting. She had facial angioedema, and corticosteroids were required to treat a concomitant exacerbation of her asthma. In her case, the comorbid medical conditions, rather than the severity of airway compromise, mandated care in the ICU.

The small number of cases in our review precludes statistical comparison with larger adult series. The small sample may reflect the rarity of this disorder in children or a methodological exclusion bias against outpatient episodes. In either case, inpatients, by definition, have more severe angioedema than outpatients; it is clear that the children in our review had less severe manifestations than those noted in adult series. Only 1 child (10%) in our series required care in the ICU, compared with 53% of adults (49/93). In addition, no children required airway intervention, which was necessary for 10% of adult patients (9/93). The angioedema in all children was treated successfully with medications.

Children with airway symptoms exhibit rapid improvement when they are treated with intravenous corticosteroids and antihistamines. This rapid resolution permits observation in the hospital ward setting with continuous pulse oximetry, rather than in the more expensive ICU setting. It is unknown whether the milder manifestations of angioedema in children are due to slower progression, earlier diagnosis, greater responsiveness to corticosteroids, or immunologic differences between children and adults. The severity of angioedema also may be influenced by the cause. The milder angioedema in children was due more often to food, while medications, specifically angiotensin-converting enzyme inhibitors, were the most commonly identified cause of the more severe adult angioedema.

The management of children with airway edema due to angioedema requires recognition of this clinically important difference from adults. Treatment algorithms based on adult series must be modified to account for the rapid improvement experienced by most children with...
pharmacological management (Figure 3). Children in acute distress require airway protection in the field, the emergency ward, or the operating room. Children with facial, palatal, or mild lingual edema who are not in immediate distress may be treated in the outpatient setting. Severe lingual and laryngeal angioedema require admission to a hospital ward or the ICU for monitoring. Safe management on a hospital ward requires adequate numbers of experienced staff to observe children at risk for airway compromise. Children whose symptoms or examination findings worsen should be transferred to the ICU or should undergo awake fiberoptic intubation in the operating room for airway protection. Tracheotomy under local anesthesia is used if intubation fails to secure the airway. Equipment for direct laryngoscopy and rigid bronchoscopy is kept ready to use. Serial airway examination, if possible, by nasopharyngolaryngoscopy documents improvement before transfer from the ICU to the ward. Pharmacological treatment is instituted immediately. Laboratory tests are ordered for recurrent unexplained episodes of angioedema or for children with a family history of hereditary angioedema. Further evaluation requires consultation with an immunologist to exclude lymphoproliferative, autoimmune, and thyroid disorders. A complete blood cell count with a differential cell count; thyroid and liver function tests; tests for antinuclear antibodies, antithyroglobulin antibodies, and antiperoxidase antibodies; an erythrocyte sedimentation rate; C2 and C4 levels; and quantitative or qualitative analysis of C1-INH are obtained.19 The diagnosis of hereditary angioedema may be determined perinatally by measuring the umbilical cord blood levels of C1-INH.20

Conversion from causative medications is made before discharge from the hospital, in coordination with the patients’ primary care providers. On discharge from the hospital, patients are given the following: (1) an epinephrine autoinjector3; (2) a recommendation to wear a medical alert bracelet10; (3) a letter to keep with them about their propensity for angioedema, as nearly one third of adult patients had more than 1 episode,5 as did 2 (20%) of the children in our review; and (4) a follow-up appointment in 2 to 4 weeks.

At follow-up, complete resolution of angioedema must be confirmed. Epidermoid and hematologic malignant neoplasms may manifest with localized edema.21,22 Persistent lesions, therefore, require further evaluation, including biopsy.

**CONCLUSIONS**

Angioedema in children is less severe than in adults. Prompt diagnosis and early treatment with an intravenous corticosteroid, an antihistamine, or subcutaneous epinephrine lead to rapid resolution and, in appropriately staffed settings, avoid the need for care in the ICU or airway intervention. Management algorithms based on adult experience must be modified to account for the milder pediatric manifestations of this immunologic disease.

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